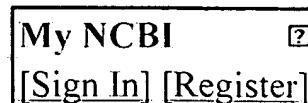


EAST Search History

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L1	1128	wallach.in. or ramakrishnan.in. or "shmushkovich.in"	US-PGPUB; USPAT	OR	OFF	2007/03/22 22:05
L2	91	I1 and (nik or (NF-kappa B-inducing kinase))	US-PGPUB; USPAT	OR	OFF	2007/03/22 22:08
L3	200	IL-2 near6 (nik or (NF-kappa B-inducing kinase))	US-PGPUB; USPAT	OR	OFF	2007/03/22 22:08
L4	2	I2 and I3	US-PGPUB; USPAT	OR	OFF	2007/03/22 22:08



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Items 81 - 95 of 95

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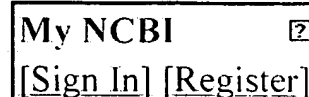
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ClinicalTrials.gov

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☐ 1: Sanchez-Valdepenas C, Martin AG, [Related Articles, Links](#)
Ramakrishnan P, Wallach D, Fresno M.

NF-kappaB-inducing kinase is involved in the activation of the CD28 responsive element through phosphorylation of c-Rel and regulation of its transactivating activity.
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J Immunol. 2002 Aug 1;169(3):1151-8.
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J Leukoc Biol. 1998 Jun;63(6):650-7. Review.
PMID: 9620655 [PubMed - indexed for MEDLINE]

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EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	"5854003".pn.	US-PGPUB; USPAT	OR	OFF	2007/03/22 20:32
L2	3	(NF-kappa B-inducing kinase or NIK) near8 (IL-2 or IL2)	US-PGPUB; USPAT	ADJ	OFF	2007/03/22 20:46

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NEWS	14	JAN 29	PHAR reloaded with new search and display fields
NEWS	15	JAN 29	CAS Registry Number crossover limit increased to 300,000 in
			multiple databases
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NEWS	19	FEB 26	MEDLINE reloaded with enhancements
NEWS	20	FEB 26	EMBASE enhanced with Clinical Trial Number field
NEWS	21	FEB 26	TOXCENTER enhanced with reloaded MEDLINE
NEWS	22	FEB 26	IFICDB/IFIPAT/IFIUDB reloaded with enhancements
NEWS	23	FEB 26	CAS Registry Number crossover limit increased from 10,000

to 300,000 in multiple databases
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MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

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L1 10 (NF-KAPPA B-INDUCING KINASE OR NIK) (8A) (IL-2 OR IL2)

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L2 4 DUPLICATE REMOVE L1 (6 DUPLICATES REMOVED)

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L2 ANSWER 1 OF 4 MEDLINE on STN DUPLICATE 1
AN 2006187607 MEDLINE
DN PubMed ID: 16585559
TI NF-kappaB-inducing kinase is involved in the activation of the
CD28 responsive element through phosphorylation of c-Rel and
regulation of its transactivating activity.
AU Sanchez-Valdepenas Carmen; Martin Angel G; Ramakrishnan
Parameswaran;
Wallach David; Fresno Manuel
CS Centro de Biologia Molecular, Consejo Superior de Investigaciones
Cientificas, Universidad Autonoma de Madrid, Madrid, Spain.
SO Journal of immunology (Baltimore, Md. : 1950), (2006 Apr 15)
Vol. 176, No.
8, pp. 4666-74.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200605
ED Entered STN: 5 Apr 2006
Last Updated on STN: 17 May 2006
Entered Medline: 16 May 2006
AB Previous evidence suggested that NF-kappaB-inducing kinase (NIK)
might regulate IL-2 synthesis. However, the molecular
mechanism is not understood. In this study, we show that NIK is
involved in CD3 plus CD28 activation of IL-2
transcription. Splenic T cells from aly/aly mice (that have a
defective
NIK protein) have a severe impairment in IL-2
and GM-CSF but not TNF secretion in response to CD3/CD28. This
effect
takes place at the transcriptional level as overexpression of
alyNIK
inhibits IL-2 promoter transcription. NIK activates the CD28
responsive element (CD28RE) of the IL-2 promoter and
strongly synergizes with c-Rel in this activity. We found that
NIK

interacts with the N-terminal domain of c-Rel, mapping this interaction to aa 771-947 of NIK. Moreover, NIK phosphorylates the c-Rel C-terminal transactivation domain (TAD) and induces Gal4-c-Rel-transactivating activity. Anti-CD28 activated Gal4-c-Rel transactivation activity, and this effect was inhibited by a NIK-defective mutant. Deletion studies mapped the region of c-Rel responsive to NIK in aa 456-540. Mutation of several serines, including Ser471, in the TAD of c-Rel abrogated the NIK-enhancing activity of its transactivating activity. Interestingly, a Jurkat mutant cell line that expresses one of the mutations of c-Rel (Ser471Asn) has a severe defect in IL-2 and CD28RE-dependent transcription in response to CD3/CD28 or to NIK. Our results support that NIK may be controlling CD28RE-dependent transcription and T cell activation by modulating c-Rel phosphorylation of the TAD. This leads to more efficient transactivation of genes which are dependent on CD28RE sites where c-Rel binds such as the IL-2 promoter.

L2 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
 AN 2003:837297 CAPLUS
 DN 139:312400
 TI Modulation of NIK with IL-2 common γ chain and therapeutic uses thereof
 IN Wallach, David; Ramakrishnan, Parameswaran; Shmushkovich, Taisia
 PA Yeda Research and Development Co.Ltd, Israel
 SO PCT Int. Appl., 98 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.
DATE	-----	----	-----	-----
PI	WO 2003087380	A1	20031023	WO 2003-IL317
	20030415			
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,			

LK, LR, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
 NZ, OM, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO,
 TR, TT, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN,
 RW: TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 AZ, BY, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
 EE, ES, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
 SK, TR, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI,
 TD, TG BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,

CA 2482387 A1 20031023 CA 2003-2482387
 20030415

AU 2003226607 A1 20031027 AU 2003-226607
 20030415

EP 1499729 A1 20050126 EP 2003-746399
 20030415

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE,
 MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU,
 SK

JP 2005530491 T 20051013 JP 2003-584319
 20030415

US 2005272633 A1 20051208 US 2005-511314
 20050517

PRAI IL 2002-149217 A 20020418
 IL 2002-152183 A 20021008
 WO 2003-IL317 W 20030415

AB This invention relates to the use of NIK and related mols. for
 the modulation of signal activities controlled by cytokines, and
 some new such mols. In addition the invention relates to the use of a DNA
 encoding NIK, or its antisense, NIK specific antibodies, a small mol. obtainable
 by screening products of combinatorial chemical in a luciferase
 system, for modulating the interaction between IL-2 common gamma
 chain (cyc) and NIK. The present invention also relates
 to the use of NIK or a mutein, variant, fusion protein,
 functional derivative, circularly permuted derivative or fragment thereof, in the
 manufacture of a medicament for the treatment of a disease, wherein a cytokine
 stimulating signalling through the IL-2 cyc is involved in the pathogenesis
 of

the disease.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2003:837291 CAPLUS

DN 139:328743

TI Modulating interaction of IL-2 with NIK by
 derivatives of the IL-2 common gamma chain, and
 therapeutic uses thereof

IN Wallach, David; Ramakrishnan, Parameswaran; Shmushkovich, Taisia

PA Yeda Research and Development Co. Ltd., Israel

SO PCT Int. Appl., 103 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.
DATE	-----	----	-----	-----

PI	WO 2003087374	A1	20031023	WO 2003-IL316
20030415				
	WO 2003087374	A9	20050127	
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	CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD,			
GE, GH,				
	GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,			
LK, LR,				
	LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO,			
NZ, OM,				
	PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN,			
TR, TT,				
	TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
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	BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,			
TD, TG				
	CA 2482718	A1	20031023	CA 2003-2482718
20030415				
	AU 2003222415	A1	20031027	AU 2003-222415
20030415				
	EP 1499724	A1	20050126	EP 2003-717504
20030415				
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MC, PT,				

IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU,

SK

JP 2005525113 T 20050825 JP 2003-584315
20030415

US 2005287144 A1 20051229 US 2005-511722
20050622

PRAI IL 2002-149217 A 20020418
IL 2002-152183 A 20021008
WO 2003-IL316 W 20030415

AB This invention relates to the use of IL-2 common gamma chain
(cyc)

and related mols. for the modulation of signal activities
controlled by

cytokines, and therapeutic uses thereof. Specifically, the
invention

relates to the use of IL-2 cyc or a mutein, variant, fusion
protein,

the intracellular domain of cyc (ICDcyc), 1-357, 1-341
functional derivative, circularly permuted derivative or
fragment thereof for

modulating the interaction between cyc and NIK. In addition the
invention relates to the use of a DNA encoding cyc or derivs.,

a DNA

encoding the antisense of cyc, an antibody specific to cyc, or
a small mol. obtainable by screening products of combinatory

chemical in a

luciferase system, for modulating the interaction between IL-
2 common gamma chain (cyc) and NIK. In another

aspect, the invention provides the use of cyc or derivs. in the
manufacture of a medicament for treatment of a disease, wherein

NIK activity is

involved in the pathogenesis of the disease.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 2

AN 2002385095 MEDLINE

DN PubMed ID: 12133934

TI Essential role of NF-kappa B-inducing kinase in T cell
activation through

the TCR/CD3 pathway.

AU Matsumoto Mitsuru; Yamada Takuji; Yoshinaga Steven K; Boone Tom;
Horan

Tom; Fujita Shigeru; Li Yi; Mitani Tasuku

CS Division of Molecular Immunology, Institute for Enzyme Research,
University of Tokushima, Tokushima, Japan..

mitsuru@ier.tokushima-u.ac.jp

SO Journal of immunology (Baltimore, Md. : 1950), (2002 Aug 1) Vol.
169, No.

3, pp. 1151-8.

Journal code: 2985117R. ISSN: 0022-1767.

CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 (RESEARCH SUPPORT, NON-U.S. GOV'T)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals
 EM 200208
 ED Entered STN: 23 Jul 2002
 Last Updated on STN: 30 Aug 2002
 Entered Medline: 13 Aug 2002
 AB NF-kappa B-inducing kinase (NIK) is involved in lymphoid
 organogenesis in
 mice through lymphotoxin-beta receptor signaling. To clarify
 the roles of
 NIK in T cell activation through TCR/CD3 and costimulation
 pathways, we
 have studied the function of T cells from aly mice, a strain
 with mutant
 NIK. NIK mutant T cells showed impaired proliferation and
 IL-2 production in response to anti-CD3 stimulation, and
 these effects were caused by impaired NF-kappa B activity in
 both mature
 and immature T cells; the impaired NF-kappa B activity in mature
 T cells
 was also associated with the failure of maintenance of activated
 NF-kappa
 B. In contrast, responses to costimulatory signals were largely
 retained
 in aly mice, suggesting that NIK is not uniquely coupled to the
 costimulatory pathways. When NIK mutant T cells were stimulated
 in the
 presence of a protein kinase C (PKC) inhibitor, proliferative
 responses
 were abrogated more severely than in control mice, suggesting
 that both
 NIK and PKC control T cell activation in a cooperative manner.
 We also
 demonstrated that NIK and PKC are involved in distinct NF-kappa B
 activation pathways downstream of TCR/CD3. These results
 suggest critical
 roles for NIK in setting the threshold for T cell activation,
 and partly
 account for the immunodeficiency in aly mice.